PPAR RECEPTOR ACTIVATOR COMPOUNDS FOR TREATING CUTANEOUS DISORDERS/AFFLICTIONS

CROSS-REFERENCE TO PRIORITY/PCT APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119 of FR-99/16270, filed December 22, 1999, and is a continuation of PCT/FR00/03646, filed December 21, 2000 and designating the United States (published in the French language on June 28, 2001 as WO 01/45664 A2; the title and abstract were also published in English), both hereby expressly incorporated by reference.

CROSS-REFERENCE TO COMPANION APPLICATION

[0002] Copending application Serial No. ____________ [Attorney Docket No. 016800-452], filed concurrently herewith and assigned to the assignee hereof.

BACKGROUND OF THE INVENTION

Technical Field of the Invention:

[0003] The present invention relates to the administration of polycyclic aromatic compounds, or cosmetic/pharmaceutical compositions comprised thereof, for the treatment of cutaneous disorders/afflictions, such as disorders of the barrier function, more particularly disorders of the secretion of epidermal lipids, photodermatoses or ulcers, and/or disorders of the metabolism of lipids.

[0004] The present invention also relates to a cosmetic/pharmaceutical regime or regimen for restoring the barrier function of the skin and more particularly for regulating the metabolism of cutaneous lipids, comprising topically

applying at least one compound of formula (I) below, more particularly as activator of receptors of PPAR type, onto the skin.

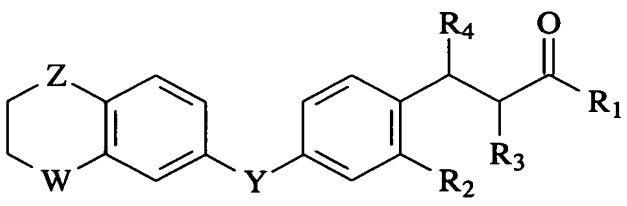
SUMMARY OF THE INVENTION

[0005] It has now unexpectedly and surprisingly been determined that certain polycyclic aromatic compounds, notably those described in EP-722,928, exhibit an antiproliferative effect and elicit marked activity with regard to the transactivation of receptors of PPAR type.

[0006] The present invention thus features administration of an effective amount of at least one polycyclic aromatic compound, more particularly as activators of receptors of PPAR type, or compositions comprised thereof, for the treatment of cutaneous disorders/afflictions such as disorders of the barrier function of the skin, more particularly disorders of the secretion of epidermal lipids, photodermatoses or ulcers, and/or disorders of the metabolism of lipids.

[0007] This invention also features a cosmetic regime/regimen for restoring the barrier function of the skin and more particularly for regulating the metabolism of cutaneous lipids, comprising topically applying at least one compound of formula (I), more particularly as activator of receptors of PPAR type, onto the skin.

[0008] The subject compounds have the structural formula (I):



(I)

in which R_1 is a hydrogen atom or an $-OR_5$ radical, wherein R_5 is as defined below; R_2 is a hydrogen atom or a lower alkyl radical; R_3 and R_4, which may be

identical or different, are each a hydrogen atom or a lower alkyl radical, with the proviso that R_2 and R_3, may together form, with the carbon atoms from which they depend, a naphthalene ring with the adjacent benzene ring; Y is an oxygen atom, an $S(O)_n$ radical or an $N\text{-}R_6$ radical, wherein n and R_6 are as defined below; Z and W, which may be identical or different, are each $-CR_7R_8-$, -O- or $-S(O)_m$, wherein m, R_7 and R_8 are as defined below; R_5 is a hydrogen atom, a linear or branched alkyl radical having from 1 to 20 carbon atoms, or a mono- or polyhydroxyalkyl radical; R_6 is a hydrogen atom or a lower alkyl radical; R_7 and R_8, which may be identical or different, are each a hydrogen atom or a lower alkyl radical; n is 0, 1 or 2; m is 0, 1 or 2; and include the salts and chiral analogs thereof. Such salts include those of an alkali or alkaline earth metal, or of zinc, or of an organic amine.

DETAILED DESCRIPTION OF BEST MODE AND SPECIFIC/PREFERRED EMBODIMENTS OF THE INVENTION

[0009] More particularly according to the present invention, by the term "lower alkyl radical" is intended a radical having 1 to 6 carbon atoms, preferably the methyl, ethyl, isopropyl, butyl, tert-butyl and hexyl radicals.

[0010] And exemplary linear or branched alkyl radicals having from 1 to 20 carbon atoms are the methyl, ethyl, propyl, 2-ethylhexyl, octyl, docecyl, hexadecyl and octadecyl radicals.

[0011] By the term "monohydroxyalkyl radical" is intended a radical having 1 to 6 carbon atoms and preferably having from 2 to 3 carbon atoms, in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical.

[0012] By the term "polyhydroxyalkyl radical" is intended a radical having from 3 to 6 carbon atoms and 2 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl and 2,3,4,5-tetrahydroxypentyl radicals and the pentaerythritol residue.

[0013] Particularly exemplary compounds of formula (I) are the following:
Compound 1: 6-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-yloxy)naphthalene-2-carboxylic acid;
Compound 2: 3-[4-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-yloxy)phenyl]acrylic acid;
Compound 3: 6-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-ylsulfanyl)naphthalene-2-carboxylic acid;
Compound 4: 3-[4-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-yloxy)phenyl]but-2-enoic acid;
Compound 5: 6-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-ylamino)naphthalene-2-carboxylic acid.

[0014] According to the present invention, the compound of formula (I) which is more particularly preferred is Compound 3: 6-(5,5,8,8-tetramethyl-5,6,7,8- tetrahydronaphth-2-ylsulfanyl)naphthalene-2-carboxylic acid.

[0015] The compounds of formula (I) can be prepared, in particular, by the methodology described in EP-722,928.

[0016] The compounds of the invention exhibit activating properties with regard to receptors of PPAR type. The receptors of PPAR type are receptors which belong to the family of steroid nuclear receptors.

[0017] By the term "activator of receptors of PPAR type" is intended any compound that exhibits in a transactivation test, such as described in Kliewer et al., Nature, 358, 771-774 (1992), an AC_{50} of less than or equal to 10 μM. The activator of receptors of PPAR type preferably exhibits an AC_{50} of less than or equal to 2 μM and advantageously of less than or equal to 1 μM.

[0018] An AC_{50} is the concentration of "activator" compound necessary to exhibit 50% of the activity of a reference molecule. This activity is determined employing an enzyme (luciferase) which is a reporter of the activation due to the compound via one of the PPAR receptors.

[0019] The activity of receptors of PPAR type is the subject of numerous studies and publications. Exemplary is the publication entitled "Differential Expression of Peroxisome Proliferator-Activated Receptor Subtypes During the Differentiation of Human Keratinocytes," Michel Rivier et al., J. Invest. Dermatol., 111, p. 1116-1121 (1998), in which a large number of bibliographic references relating to receptors of PPAR type are listed.

[0020] The use of activators of receptors of PPAR-α type for restoring the barrier function and more particularly disorders of the secretion of epidermal lipids, promoting epidermal differentiation and inhibiting epidermal proliferation, is described in WO 98/32444.

[0021] Furthermore, the administration of activators of receptors of PPAR-α and/or PPAR-γ type for treating cutaneous disorders related to an anomaly in the differentiation of epidermal cells has been described by Michel Rivier et al., J. Invest. Dermatol., 111, p. 1116-1121 (1998).

[0022] It has also been described in WO 96/33724, that compounds which are selective for PPAR-γ receptors, such as a prostaglandin-J2 or -D2, are potential active principles for the treatment of obesity and diabetes.

[0023] Pharmaceutical compositions comprising at least one compound of formula (I) are thus well suited for the treatment of cutaneous disorders/afflictions, such as disorders of the skin barrier function, more particularly disorders of the secretion of epidermal lipids, photodermatoses or ulcers, and/or disorders of the metabolism of lipids.

[0024] Particulary exemplary disorders of the barrier function of the skin are, more especially, disorders of the secretion of epidermal lipids, of skin disorders in premature babies born before 33 weeks, chapped lips or blisters resulting from mechanical friction.

[0025] Exemplary ulcers are ulcers and erosions due to chemical or thermal burns, bullous disorders or vascular or ischaemia disorders, including venous, arterial, embolic or diabetic ulcers.

[0026] And exemplary conditions of the metabolism of lipids are obesity, hyperlipidaemia or non-insulin-dependent diabetes.

[0027] The compositions according to the invention can be administered via the enteral, parenteral or topical or ocular route, for such period of time as required to elicit the desired response. The pharmaceutical compositions are preferably packaged in a form suitable for application by the topical route.

[0028] The subject compositions, more particularly the pharmaceutical compositions, can be provided, for the enteral route, in the form of tablets, including sugar-coated tablets, hard gelatin capsules, syrups, suspensions, solutions, powders, granules, emulsions or lipid or polymeric microspheres or nanospheres or vesicles which permit controlled release. The subject compositions can be provided, for the parenteral route, in the form of solutions or suspensions for infusion or for injection.

[0029] The subject compounds according to the invention are generally administered at a daily dose of approximately 0.001 mg/kg to 100 mg/kg of body weight, taken on 1 to 3 occasions.

[0030] The pharmaceutical compositions according to the invention, for the topical route, are more preferably for the treatment of the skin and mucous membranes and can be provided in the form of salves, creams, emulsions, milks, ointments, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. Same can also be provided in the form of lipid or polymeric microspheres or nanospheres or vesicles or of polymeric patches and hydrogels which permit controlled release. The compositions for topical application can be provided either in anhydrous form or in aqueous form.

[0031] The subject compounds are administered via the topical route at a concentration generally ranging from 0.001% to 10% by weight, preferably from 0.01 to 1% by weight, with respect to the total weight of the composition.

[0032] The compounds of formula (I) according to the invention also find application in the cosmetics field, in particular in body and hair hygiene and more

particularly for restoring the barrier function of the skin and more particularly for regulating and/or restoring the metabolism of cutaneous lipids. In comparison with the products known previously, these compounds of formula (I) present the advantage of additionally exhibiting other advantageous properties, in particular anti-inflammatory or soothing properties, which makes them less irritating and therefore better tolerated compounds.

[0033] The cosmetic compositions according to the invention, comprising, in a cosmetically acceptable vehicle, diluent or carrier, at least one compound of formula (I), one of its optical or geometrical isomers or one of its salts, can be provided, in particular, in the form of a cream, milk, lotion, emulsion, gel, lipid or polymeric microspheres or nanospheres or vesicles, soap or shampoo.

[0034] The concentration of compound of formula (I) in the cosmetic compositions advantageously ranges from 0.001% to 3% by weight.

[0035] The compositions according to the present invention can, of course, additionally comprise inert or even pharmacodynamically active additives or adjuvants, or combinations of these additives and adjuvants, and in particular: wetting agents; depigmenting agents, such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents, such as glycerol, PEG 400, thiamorpholinone and derivatives thereof, or urea; antiseborrhoeic or antiacne agents, such as S-carboxymethylcysteine, S-benzylcysteamine, their salts or derivatives thereof, or benzoyl peroxide; antifungal agents, such as ketoconazole or 4,5- polymethylene-3-isothiazolidones; antibacterials; carotenoids and in particular β-carotene; antipsoriatic agents, such as anthralin and derivatives thereof; eicosa-5,8,11,14- tetraynoic and eicosa-5,8,11-triynoic acids, their esters and amides, and also the retinoids. The subject compounds of formula (I) can also be formulated with vitamins D or derivatives thereof, with corticosteroids, with agents for combating free radicals, with α-hydroxy or α-keto acids or derivatives thereof, or with ion channel blockers.

[0036] These compositions can also comprise flavor-improving agents, preservatives, such as esters of para-hydroxybenzoic acid, stabilizing agents, moisture-regulating agents, pH-regulating agents, agents for modifying osmotic pressure, emulsifying agents, UV-A and UV-B screening agents, or antioxidants, such as α-tocopherol, butylhydroxyanisole or butylhydroxy-toluene.

[0037] One skilled in this art will of course take care to select the optional compound or compounds to be added to these compositions such that the advantageous properties intrinsically associated with the present invention are not, or not substantially, detrimentally affected by the envisaged addition.

[0038] In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in nowise limitative.

[0039] In said examples to follow, all parts and percentages are given by weight, unless otherwise indicated.

EXAMPLE 1:

[0040] Various results of biological tests which illustrate the properties of transactivation of PPAR receptors of the compounds of the invention are reported in these examples.

[0041] The comparative examples correspond to compounds which are disclosed in EP-722,928 but which do not verify the conditions of the compounds of formula (I).

[0042] The biological tests carried out correspond to those described above. The method used to determine the AC_{50} values was that described in Kliewer et al., Nature, 358, 771-774 (1992). Thus, the activating power via PPAR-α, PPAR-γ or PPAR-δ of molecules can be evaluated with a transactivation test in which HeLa cells were cotransfected with an expression vector encoding these receptors and a reporter plasmid comprising a PPRE response element

cloned upstream of a portion of a promoter of the SV40 virus and of the luciferase gene. The cotransfected cells were treated for 24 hours with the molecules to be tested and the activity of the luciferase was determined by luminescence.

[0043] Reference 1, the reference molecule for PPAR-α receptors, was [4-chloro-6-(2,3-dimethyl-phenylamino) pyrimidin-2-ylsulfanyl]acetic acid; Reference 2, the reference molecule for PPAR-δ and PPAR-γ receptors, was 5-{4-[2-(methylpyrid-2- ylamino)ethoxy]benzyl}thiazolidine-2,4-dione.

[0044] Comparative Example 1 was 2-methyl-4-[4- (5,5,8,8,-tetramethyl-5,6,7,8-tetrahydronaphth-2-yloxy)benzylidine]-4H-oxazol-5-one. Comparative Example 2 was 2-acetylamino-3-[4-(5,5,8,8- tetramethyl-5,6,7,8-tetrahydronaphth-2-yloxy)phenyl]-acrylic acid.

[0045] The results obtained in the tests of transactivation of receptors of PPAR type are combined in the following table:

Compounds	α	γ	β
Reference 1	100* (1.4)**	n.a	n.a
Reference 2	n.a	100(0.07)	100(0.13)
Compound 1	18	23	152(0.7)
Compound 2	12	18	204(0.9)
Compound 3	24	40	172(0.2)
Compound 4	12	0	56
Compound 5	25	69	328(7)
Comparative Example 1	5	0	7
Comparative Example 2	7	4	0

n.a connotes "non active"

* % of activation

() ** AC_{50} in μM

[0046] These results evidence the activation of the compounds of the invention for the various subtypes of receptors of PPAR type: PPAR-α, PPAR-β and PPAR-γ.

EXAMPLE 2:

[0047] Various specific compositions based on the compounds according to the invention were formulated:

A - ORAL ROUTE:

[0048] **(a) 0.2 g tablet:**

Compound 1	0.001g
Starch	0.114g
Dicalcium phosphate	0.020g
Silica	0.020g
Lactose	0.030g
Talc	0.010g
Magnesium stearate	0.005g

[0049] **(b) Oral suspension in 5 ml vials:**

Compound 5		0.001g
Glycerol		0.500g
70% Sorbitol		0.500g
Sodium saccharin		0.010g
Methyl para-hydroxybenzoate		0.040g
Flavoring	q.s.	
Purified water	q.s. for	0.001g

[0050] **(c) 0.8 g tablet:**

Compound 2		0.500g
Pregelatinized starch		0.100g
Microcrystalline cellulose		0.115g
Lactose		0.075g
Magnesium stearate		0.010g

[0051] **(d) Oral suspension in 10 ml vials:**

Compound 4		0.200g
Glycerol		1.000g
70% Sorbitol		1.000g
Sodium saccharin		0.010g
Methyl para-hydroxybenzoate		0.080g
Flavoring	q.s.	
Purified water	q.s. for	10ml

B - TOPICAL ROUTE:

[0052] **(a) Salve:**

Compound 1		0.020g
Isopropyl myristate		81.700g
Fluid liquid petrolatum		9.100g
Silica ("Aerosil 200" marketed by Degussa)		0.020g

[0053] **(b) Salve:**

Compound 2		0.300g
White petrolatum, pharmaceutical grade	q.s. for	100g

[0054] **(c) Nonionic water-in-oil cream:**

Compound 1		0.100g
Mixture of emulsified lanolin alcohols, of waxes and of oils ("Anhydrous Eucerin", marketed by BDF)		39.900g
Methyl para-hydroxybenzoate		0.075g
Propyl para-hydroxybenzoate		0.075g
Sterile demineralized water	q.s. for	100g

[0055] **(d) Lotion:**

Compound 3		0.100g
Polyethylene glycol (PEG 400)		69.900g
95% Ethanol		30.000g

[0056] **(e) Hydrophobic salve:**

Compound 5		0.300g
Isopropyl myristate		36.400g
Silicone oil ("Rhodorsil 47 V 300", marketed by Rhône-Poulenc)		36.400g
Beeswax		13.600g
Silicone oil ("Abil 300.000 cst" marketed by Goldschmidt)	q.s. for	100g

[0057] **(f) Nonionic oil-in-water cream:**

Compound 2		1.000g
Cetyl alcohol		4.000g
Glyceryl monostearate		2.500g
PEG 50 stearate		2.500g
Karite butter		9.200g

Propylene glycol		2.000g
Methyl para-hydroxybenzoate		0.075g
Propyl para-hydroxybenzoate		0.075g
Sterile demineralized water	q.s. for	100g

[0058] While the invention has been described in terms of various specific and preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof.